ORIGINAL ARTICLE

Oxygen Therapy in Suspected Acute Myocardial Infarction

Robin Hofmann, M.D., Stefan K. James, M.D., Ph.D., Tomas Jernberg, M.D., Ph.D., Bertil Lindahl, M.D., Ph.D., David Erlinge, M.D., Ph.D., Nils Witt, M.D., Ph.D., Gabriel Arefalk, M.D., Mats Frick, M.D., Ph.D., Joakim Alfredsson, M.D., Ph.D., Lennart Nilsson, M.D., Ph.D., Annica Ravn-Fischer, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thomas Kellerth, M.D., David Sparv, B.Sc., Ulf Ekelund, M.D., Ph.D., Rickard Linder, M.D., Ph.D., Mattias Ekström, M.D., Ph.D., Jörg Lauermann, M.D., Urban Haaga, B.Sc., John Pernow, M.D., Ph.D., Ollie Östlund, Ph.D., Johan Herlitz, M.D., Ph.D., and Leif Svensson, M.D., Ph.D., for the DETO2X–SWEDEHEART Investigators*

ABSTRACT

BACKGROUND

The clinical effect of routine oxygen therapy in patients with suspected acute myocardial infarction who do not have hypoxemia at baseline is uncertain.

METHODS

In this registry-based randomized clinical trial, we used nationwide Swedish registries for patient enrollment and data collection. Patients with suspected myocardial infarction and an oxygen saturation of 90% or higher were randomly assigned to receive either supplemental oxygen (6 liters per minute for 6 to 12 hours, delivered through an open face mask) or ambient air.

RESULTS

A total of 6629 patients were enrolled. The median duration of oxygen therapy was 11.6 hours, and the median oxygen saturation at the end of the treatment period was 99% among patients assigned to oxygen and 97% among patients assigned to ambient air. Hypoxemia developed in 62 patients (1.9%) in the oxygen group, as compared with 254 patients (7.7%) in the ambient-air group. The median of the highest troponin level during hospitalization was 946.5 ng per liter in the oxygen group and 983.0 ng per liter in the ambient-air group. The primary end point of death from any cause within 1 year after randomization occurred in 5.0% of patients (166 of 3311) assigned to oxygen and in 5.1% of patients (168 of 3318) assigned to ambient air (hazard ratio, 0.97; 95% confidence interval [CI], 0.79 to 1.21; P=0.80). Rehospitalization with myocardial infarction within 1 year occurred in 126 patients (3.8%) assigned to oxygen and in 111 patients (3.3%) assigned to ambient air (hazard ratio, 1.13; 95% CI, 0.88 to 1.46; P=0.33). The results were consistent across all predefined subgroups.

CONCLUSIONS

Routine use of supplemental oxygen in patients with suspected myocardial infarction who did not have hypoxemia was not found to reduce 1-year all-cause mortality. (Funded by the Swedish Heart–Lung Foundation and others; DETO2X-AMI ClinicalTrials.gov number, NCT01787110.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Hofmann at Karolinska Institutet, Department of Clinical Science and Education, Division of Cardiology, Södersjukhuset, Sjukhusbacken 10, 11883 Stockholm, Sweden, or at robin.hofmann@sll.se.

*A complete list of the DETO2X–SWEDEHEART Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 28, 2017, at NEJM.org.

N Engl J Med 2017;377:1240-9.
DOI: 10.1056/NEJMoa1706222

Copyright © 2017 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Myocardial infarction is caused by a mismatch of oxygen and substrate supply and demand in the myocardium that leads to ischemia and ultimately to cell death. Therefore, for more than a century, supplemental oxygen has been used routinely in the treatment of patients with suspected acute myocardial infarction[1] and is recommended in clinical guidelines.[2,3] The rationale behind oxygen therapy is to increase oxygen delivery to the ischemic myocardium and thereby limit infarct size and subsequent complications. The basis for this practice is limited to experimental laboratory data and small clinical studies.[4-6] However, above-normal oxygen levels in the blood can cause coronary vasoconstriction[7] and increase the production of reactive oxygen species,[8] potentially contributing to reperfusion injury. Such a negative effect is supported by the Australian Air Versus Oxygen in Myocardial Infarction (AVOID) trial, which reported larger infarct sizes in patients with ST-segment elevation myocardial infarction (STEMI) who received oxygen than in those who did not receive oxygen.[9] Furthermore, an updated Cochrane report[10] from 2016 did not show any evidence supporting the routine use of oxygen in the treatment of patients with myocardial infarction. Trials powered to assess hard clinical end points with regard to oxygen use in this context are lacking. Thus, the efficacy of routine oxygen therapy in patients with myocardial infarction remains highly uncertain.

We therefore conducted a registry-based randomized clinical trial to evaluate the effect of oxygen therapy on all-cause mortality at 1 year among patients with suspected myocardial infarction who did not have hypoxemia at baseline.

METHODS

TRIAL DESIGN

The Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) trial was a multicenter, parallel-group, open-label, registry-based, randomized, controlled trial in which routine supplemental oxygen therapy was compared with ambient air in the treatment of patients with suspected myocardial infarction who did not have hypoxemia at baseline. The trial used the national comprehensive Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) (see the Supplementary Appendix, available with the full text of this article at NEJM.org)[11] for patient enrollment and data collection.

A Quick Take is available at NEJM.org

The trial design and methods have been described and published previously.[12] Approval of the protocol was obtained from the regional ethics review board in Gothenburg and the Swedish Medical Products Agency. The trial sponsor was the Karolinska Institutet. Trial and data management, monitoring, and statistical analyses were performed at the Uppsala Clinical Research Center at Uppsala University. The trial was conducted and the manuscript written by the authors (details are provided in the Supplementary Appendix), who decided to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and all analyses and for the fidelity of the trial to the protocol and statistical analysis plan, which are available at NEJM.org. The funding agencies had no access to the trial data and no role in the trial design, implementation, or reporting. No sponsorship or funding from industry or for-profit sources was received for the trial.

PATIENTS

Patients who presented to the ambulance services, emergency departments, coronary care units, or catheterization laboratories of participating hospitals were evaluated for eligibility. Trial participants were required to be 30 years of age or older and to have symptoms suggestive of myocardial infarction (defined as chest pain or shortness of breath) for less than 6 hours, an oxygen saturation of 90% or higher on pulse oximetry, and either electrocardiographic changes indicating ischemia[13] or elevated cardiac troponin T or I levels on admission (i.e., above the locally defined decision limit for the identification of myocardial infarction). To allow complete follow-up through the Swedish National Population Registry, only Swedish citizens who had a unique personal identification number were enrolled.

Patients who were receiving ongoing oxygen therapy, as well as those who presented with a cardiac arrest or had a cardiac arrest between presentation and enrollment (for whom high-flow oxygen therapy would normally be provided), were excluded. If supplemental oxygen therapy had been administered for less than 20 minutes before evaluation for enrollment, a new evaluation was allowed after discontinuation of oxygen delivery and 10 minutes of washout.

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

TRIAL PROCEDURES

Patients who met all inclusion criteria and no exclusion criteria were asked to provide oral consent followed by written confirmation within 24 hours, as described in the Supplementary Appendix. After oral consent was obtained, patients were randomly assigned to receive either oxygen therapy (at 6 liters per minute for 6 to 12 hours delivered through an open face mask) or ambient air. Unrestricted 1:1 randomization following a computer-generated list was performed with the use of an online randomization module embedded in SWEDEHEART. For patients in the oxygen group, oxygen therapy was initiated directly on site immediately after randomization.

Any treatment outside the trial protocol was left to the discretion of the treating physician. Oxygen saturation was documented at the beginning and at the end of the treatment period. If it was deemed clinically necessary, particularly in cases of hypoxemia (defined as an oxygen saturation <90%) caused by circulatory or respiratory failure, supplemental oxygen outside the protocol was provided, which was reported separately.

END POINTS AND FOLLOW-UP

The primary end point was death from any cause within 365 days after randomization, assessed in the intention-to-treat population. Secondary end points included death from any cause within 30 days after randomization, rehospitalization with myocardial infarction, rehospitalization with heart failure, and cardiovascular death (as described in the Supplementary Appendix), as well as composites of these end points, assessed at 30 days and 365 days.

Analyses of death, rehospitalization with myocardial infarction, and the composite of death or rehospitalization with myocardial infarction are included in this report. Data on the end points of rehospitalization with heart failure and cardiovascular death are not available from SWEDEHEART and must be obtained from the Swedish National Inpatient and Outpatient Registries. Owing to a delay of up to 12 months from the date of database lock for the Swedish National Board of Health and Welfare to make these data available, analyses of these end points are not included in this report.

Mortality data were obtained from the Swedish National Population Registry, which includes the vital status of all Swedish citizens. All other variables were obtained from SWEDEHEART, which is monitored on a regular basis.[11] Diagnoses at discharge are listed according to codes from the *International Classification of Diseases, 10th Revision* (ICD-10).

The end of follow-up was December 30, 2016, which was 365 days after the last patient underwent randomization. To allow for any lag in registry reporting, the final database was extracted from SWEDEHEART on February 28, 2017, including data on any linked deaths that occurred through December 30, 2016, and reported in the population registry as of February 14, 2017. Five patients who were never included in SWEDEHEART were followed up manually for data on mortality by the investigators in January 2017. No central adjudication or trial-specific patient follow-up was performed.

Through restriction of access to the randomization list to authorized SWEDEHEART personnel, the trial team and steering committee were kept unaware of the study-group assignments until the locking of the database. Accumulated data without study-group information were available for the monitoring of progress throughout the trial.

STATISTICAL ANALYSIS

The sample size was calculated from published data[14,15] and analyses from SWEDEHEART for the years 2005 through 2010. The 1-year total mortality among patients with myocardial infarction was estimated to be 14.4%. A clinically relevant effect of supplemental oxygen was defined as a 20% lower relative risk of death from any cause within 1 year in the oxygen group than in the ambient-air group. With the chi-square test, to be able to reject the null hypothesis at a significance level of 0.05 (two-sided) with a power of 0.90, a total of 2856 patients per group were needed. To control for patients crossing over or not completing the trial, the planned sample size was increased to 3300 patients per group, which resulted in a total of 6600 patients.

The results were analyzed according to the intention-to-treat principle.[16] Randomization numbers assigned unintentionally, such as by clicking the wrong box or randomly assigning the wrong patient record in SWEDEHEART, were recorded in the clean file documentation and removed from the analysis database. A supplementary per-protocol analysis was conducted in which patients were excluded if they were

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

reported as having not completed participation in the trial through the end of the treatment period, unless the noncompletion was due to hypoxemia.

The time-to-event analysis of death from any cause within 365 days after randomization is presented as Kaplan–Meier curves. Hazard ratios were calculated with the use of a Cox proportional-hazards model, with adjustment for age in years (as a linear covariate on the log-hazard scale) and sex.[17] Estimates of differences between the study groups are presented with two-tailed 95% confidence intervals and associated P values. A two-tailed P value of less than 0.05 was considered to indicate statistical significance. Eleven prespecified subgroup analyses (as defined in the Supplementary Appendix) were performed with the use of proportional-hazards models with adjustment for age and sex and formal tests for interaction. All analyses were conducted with SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

Of the 69 hospitals in Sweden with acute cardiac care facilities, 35 participated in the trial. Between April 13, 2013, and December 30, 2015, a total of 6629 patients with suspected myocardial infarction were enrolled and included in the intention-to-treat analysis (Fig. 1). Twenty-one randomization numbers that were assigned by mistake were discarded.

Overall, 6243 patients (94.2%) were enrolled because of chest pain, and 140 patients (2.1%) were enrolled because of shortness of breath. A total of 4433 patients (66.9%) arrived at the hospital by ambulance. The median time from symptom onset to randomization (data were available for 5685 patients) was 245 minutes in the oxygen group and 250 minutes in the ambient-air group (Table 1).

The baseline characteristics and clinical presentation of all the patients, as well as the final diagnoses, are provided in Table 1. The final diagnosis was myocardial infarction in 5010 patients (75.6%) (including 2952 patients [44.5%] with STEMI), angina pectoris in 374 (5.6%), other cardiac disease in 511 (7.7%), pulmonary disease in 32 (0.5%), unspecified chest pain in 492 (7.4%), and another, noncardiovascular condition in 210 (3.2%).

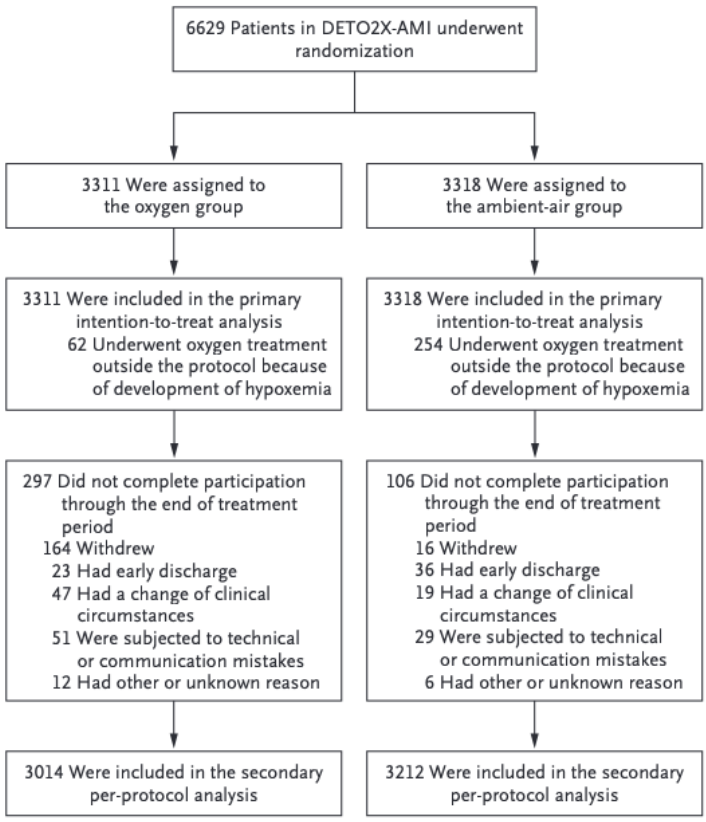

Figure 1. Enrollment, Randomization, and Analysis.

Eligible patients with suspected myocardial infarction who presented to the ambulance service, emergency departments, coronary care units, or catheterization laboratories of participating hospitals were evaluated for inclusion. Shown are the numbers of patients who were enrolled in the trial, randomly assigned to a study group, and followed up during the trial period. DETO2X-AMI denotes Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction trial.

PROCEDURAL DATA

Data on medication, procedures, and complications during the hospitalization period are provided in Table 2. At the time of randomization, the median oxygen saturation was 97%. Overall, 3311 patients were assigned to receive oxygen and 3318 patients were assigned to receive ambient air. The median duration of oxygen therapy was 11.64 hours, with a median oxygen saturation at the end of the treatment period of 99% among patients assigned to oxygen and 97% among patients assigned to ambient air (P<0.001).

In total, 316 patients (4.8%) received supplemental oxygen outside the trial because of the development of hypoxemia (resulting from any cause, including cardiac arrest or circulatory or respiratory failure), including 62 patients (1.9%) assigned to oxygen and 254 patients (7.7%) as-

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Table 1. Baseline Characteristics, Clinical Presentation, and Final Diagnoses.*

Characteristic	Oxygen Group (N=3311)		Ambient-Air Group (N=3318)	
	Value among Patients with Data Available	No. (%) of Patients with Missing Data	Value among Patients with Data Available	No. (%) of Patients with Missing Data
Median age (IQR) — yr	68.0 (59.0–76.0)	0	68.0 (59.0–76.0)	0
Male sex — no. (%)	2264 (68.4)	0	2342 (70.6)	0
Body-mass index†	27.1±4.4	92 (2.8)	27.2±4.4	105 (3.2)
Current smoker — no. (%)	704 (21.3)	129 (3.9)	721 (21.7)	127 (3.8)
Hypertension — no. (%)	1575 (47.6)	42 (1.3)	1559 (47.0)	39 (1.2)
Diabetes mellitus — no. (%)	589 (17.8)	24 (0.7)	644 (19.4)	31 (0.9)
Previous cardiovascular disease — no. (%)				
Myocardial infarction	682 (20.6)	29 (0.9)	667 (20.1)	33 (1.0)
PCI	525 (15.9)	36 (1.1)	549 (16.5)	37 (1.1)
CABG	208 (6.3)	32 (1.0)	206 (6.2)	36 (1.1)
Cause of admission — no. (%)		28 (0.8)		30 (0.9)
Chest pain	3123 (94.3)		3120 (94.0)	
Dyspnea	63 (1.9)		77 (2.3)	
Cardiac arrest	1 (<0.1)		1 (<0.1)	
Medication at admission — no. (%)				
Aspirin	904 (27.3)	44 (1.3)	961 (29.0)	49 (1.5)
$P2Y_{12}$ receptor inhibitor	177 (5.3)	43 (1.3)	173 (5.2)	51 (1.5)
Beta-blocker	1030 (31.1)	54 (1.6)	1052 (31.7)	58 (1.7)
Statin	884 (26.7)	48 (1.4)	895 (27.0)	47 (1.4)
ACE inhibitor or angiotensin II blocker	1186 (35.8)	55 (1.7)	1237 (37.3)	62 (1.9)
Calcium blocker	617 (18.6)	53 (1.6)	615 (18.5)	59 (1.8)
Diuretic	543 (16.4)	55 (1.7)	525 (15.8)	54 (1.6)
Median time from symptom onset to randomization (IQR) — min	245.0 (135.0–450.0)	481 (14.5)	250 (134.0–458.0)	463 (14.0)
Ambulance transportation — no. (%)	2215 (66.9)	47 (1.4)	2218 (66.8)	39 (1.2)
Vital signs at presentation				
Systolic blood pressure — mm Hg‡	150.3±27.8	28 (0.8)	148.7±28.0	28 (0.8)
Heart rate — beats/min	78.6±19.3	27 (0.8)	78.1±19.5	27 (0.8)
Median oxygen saturation (IQR) — %	97 (95–98)	0	97 (95–98)	0
Final diagnosis — no. (%)§		0		0
Myocardial infarction	2485 (75.1)		2525 (76.1)	
STEMI	1431 (43.2)		1521 (45.8)	
Angina pectoris	189 (5.7)		185 (5.6)	
Other cardiac diagnosis	254 (7.7)		257 (7.7)	
Atrial fibrillation	52 (1.6)		44 (1.3)	
Heart failure	43 (1.3)		40 (1.2)	
Cardiomyopathy	48 (1.4)		46 (1.4)	
Perimyocarditis	32 (1.0)		43 (1.3)	
Pulmonary embolism	7 (0.2)		9 (0.3)	

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Table 1. (Continued.)

Characteristic	Oxygen Group (N=3311)		Ambient-Air Group (N=3318)	
	Value among Patients with Data Available	No. (%) of Patients with Missing Data	Value among Patients with Data Available	No. (%) of Patients with Missing Data
Pulmonary disease	17 (0.5)		15 (0.5)	
Pneumonia	8 (0.2)		7 (0.2)	
COPD or asthma	2 (0.1)		2 (0.1)	
Unspecified chest pain	258 (7.8)		234 (7.1)	
Other, noncardiovascular diagnosis	108 (3.3)		102 (3.1)	
Musculoskeletal pain	7 (0.2)		14 (0.4)	

* Plus–minus values are means ±SD. There were no significant differences in baseline characteristics between the oxygen group and the ambient-air group, except as otherwise noted. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, IQR interquartile range, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The difference between the oxygen group and the ambient-air group was significant (P<0.05).
§ The most common diagnoses are shown. Final diagnoses were classified according to the *International Classification of Diseases, 10th Revision* (ICD-10). The ICD-10 code or codes included in the final diagnoses were as follows: angina pectoris, I.20; atrial fibrillation, I.48; cardiomyopathy, I.42; COPD or asthma, J44 and J45; heart failure, I.50; myocardial infarction, I.21 and I.22; musculoskeletal pain, M.54 and M.79; other cardiac diagnosis, I codes other than I.20, I.21, and I.22; perimyocarditis, I.30 and I.40; pneumonia, J.15 and J.16; pulmonary disease, J codes; pulmonary embolism, I.26; and unspecified chest pain, R.07.

signed to ambient air (P<0.001). An additional 403 (6.1%) patients did not complete participation in the trial in their randomly assigned study group through the end of the treatment period, including 297 patients assigned to oxygen (the most common reason for noncompletion was the patient declining to continue oxygen therapy) and 106 patients assigned to ambient air (Fig. 1, and the Supplementary Appendix). The per-protocol analysis included 3014 patients (91.0%) assigned to oxygen and 3212 patients (96.8%) assigned to ambient air (Fig. 1). Intravenous inotropic agents were used in 46 patients (1.4%) assigned to oxygen and 70 patients (2.1%) assigned to ambient air (P=0.02).

CLINICAL OUTCOMES

Follow-up data on mortality were obtained for all patients from the records of the Swedish National Population Registry (see the Supplementary Appendix). Among patients who were randomly assigned to receive oxygen, 5.0% (166 of 3311) died within 1 year after randomization, as compared with 5.1% (168 of 3318) randomly assigned to ambient air (hazard ratio, 0.97; 95% confidence interval [CI], 0.79 to 1.21; P=0.80) (Fig. 2 and Table 3, and Fig. S1 in the Supplementary Appendix). The corresponding 1-year mortality in the per-protocol population was 4.7% (141 of 3014) and 5.1% (163 of 3212), respectively (hazard ratio, 0.91; 95% CI, 0.72 to 1.14; P=0.40) (Fig. S1 in the Supplementary Appendix). The findings for the primary end point were consistent across all prespecified subgroups (Fig. S1 in the Supplementary Appendix).

Rehospitalization with myocardial infarction within 1 year occurred in 126 patients (3.8%) assigned to the oxygen group and 111 patients (3.3%) assigned to the ambient-air group (hazard ratio, 1.13; 95% CI, 0.88 to 1.46; P=0.33). The composite end point of death from any cause or rehospitalization with myocardial infarction occurred in 275 patients (8.3%) in the oxygen group and 264 patients (8.0%) in the ambient-air group (hazard ratio, 1.03; 95% CI, 0.87 to 1.22; P=0.70). No significant difference between the two groups was detected at 30 days with regard to death, rehospitalization with myocardial infarction, or the composite of these two end points. Data on the highest measured level of highly sensitive cardiac troponin T during hospitalization were available for 3976 of 5010 patients (79.4%) with confirmed myocardial infarction, and this measure did not differ significantly between the study groups (Table 3, and Fig. S2 in the Supplementary Appendix).

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Table 2. Data on Procedures, Medication, and Complications during Hospitalization.*

Variable	Oxygen Group (N=3311)		Ambient-Air Group (N=3318)		P Value
	Value among Patients with Data Available	No. (%) of Patients with Missing Data	Value among Patients with Data Available	No. (%) of Patients with Missing Data	
Median duration of oxygen therapy (IQR) — hr	11.64 (6.03–12.02)	243 (7.3)	—	—	
Received oxygen outside the protocol because of development of hypoxemia — no. (%)	62 (1.9)	0	254 (7.7)	0	<0.001
Median oxygen saturation at end of treatment period (IQR) — %	99 (97–100)	569 (17.2)	97 (95–98)	563 (17.0)	<0.001
Procedures — no. (%)					
Coronary angiography	2797 (84.5)	0	2836 (85.5)	0	0.26
PCI	2183 (65.9)	0	2246 (67.7)	0	0.13
CABG	96 (2.9)	24 (0.7)	110 (3.3)	28 (0.8)	0.51
Median duration of hospital stay (range) — days	3.0 (0–68)	0	3.0 (0–95)	0	0.87
Medication — no. (%)					
Intravenous diuretic	309 (9.3)	30 (0.9)	322 (9.7)	38 (1.1)	0.58
Intravenous inotrope†	46 (1.4)	33 (1.0)	70 (2.1)	42 (1.3)	0.02
Intravenous nitroglycerin	252 (7.6)	32 (1.0)	221 (6.7)	44 (1.3)	0.14
Aspirin	2758 (83.3)	54 (1.6)	2803 (84.5)	55 (1.7)	0.16
$P2Y_{12}$ receptor inhibitor	2445 (73.8)	53 (1.6)	2463 (74.2)	54 (1.6)	0.62
Beta-blocker	2702 (81.6)	54 (1.6)	2752 (82.9)	52 (1.6)	0.13
Statin	2782 (84.0)	53 (1.6)	2765 (83.3)	55 (1.7)	0.46
ACE inhibitor or ARB	2586 (78.1)	53 (1.6)	2557 (77.1)	55 (1.7)	0.32
Calcium blocker	519 (15.7)	52 (1.6)	547 (16.5)	54 (1.6)	0.36
Diuretic	607 (18.3)	53 (1.6)	615 (18.5)	53 (1.6)	0.82
Complications — no. (%)					
Reinfarction	17 (0.5)	34 (1.0)	15 (0.5)	33 (1.0)	0.72
New-onset atrial fibrillation	94 (2.8)	33 (1.0)	103 (3.1)	32 (1.0)	0.53
Atrioventricular block, second-degree or third-degree	46 (1.4)	30 (0.9)	58 (1.7)	30 (0.9)	0.24
Cardiogenic shock	32 (1.0)	27 (0.8)	37 (1.1)	27 (0.8)	0.54
Cardiac arrest	79 (2.4)	28 (0.8)	63 (1.9)	28 (0.8)	0.17
Death	53 (1.6)	28 (0.8)	44 (1.3)	26 (0.8)	0.35

* Plus–minus values are means ±SD. ARB denotes angiotensin-receptor blocker.
† P<0.05 for the comparison between the oxygen group and the ambient-air group.

OUTCOMES AMONG PATIENTS NOT ENROLLED IN THE TRIAL

During the trial period, a total of 22,872 patients with confirmed myocardial infarction were reported in the SWEDEHEART registry at participating sites, of whom 5010 (21.9%) were enrolled in the DETO2X-AMI trial. The remaining 17,862 patients with confirmed myocardial infarction who did not undergo randomization were at higher risk for all the end points we considered (Table S1 in the Supplementary Appendix), were more often admitted with dyspnea and after cardiac arrest, and had considerably worse outcomes (Table S2 in the Supplementary

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

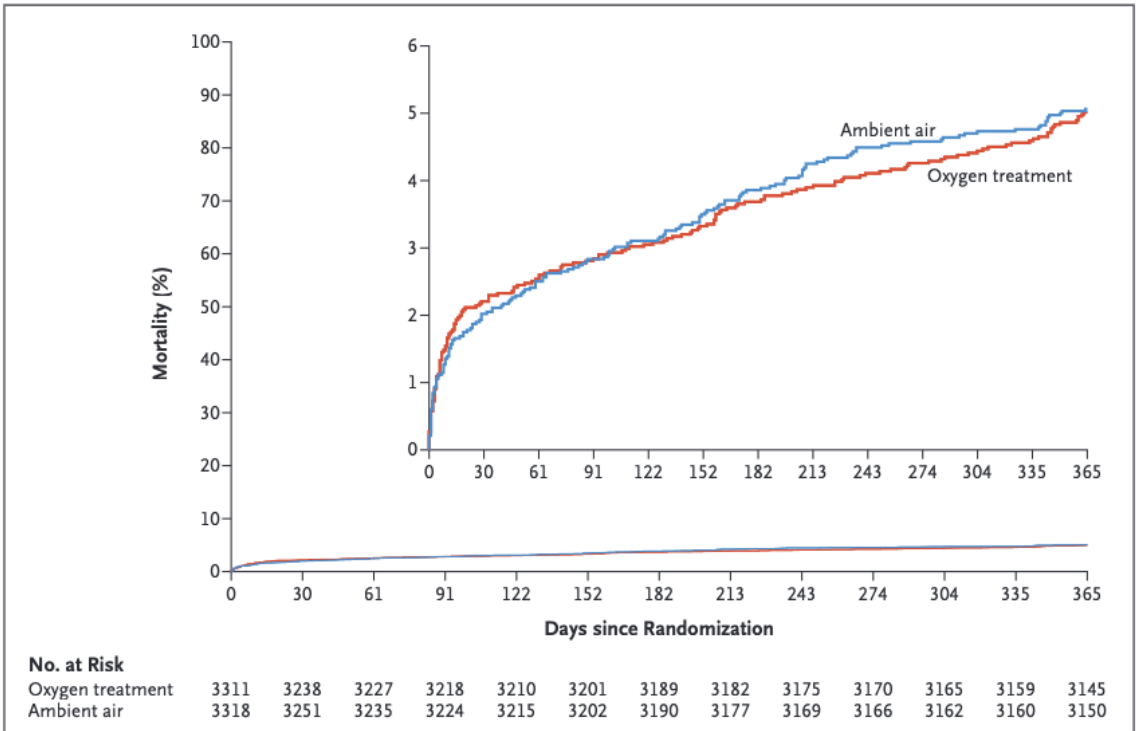

Figure 2. Kaplan–Meier Curves for Death from Any Cause.

Kaplan–Meier curves are shown for the cumulative probability of death from any cause up to 365 days after randomization among patients assigned to oxygen or ambient air. The proportional-hazards assumption was subjected to post hoc testing by inserting a linear treatment–time interaction in the Cox proportional-hazards model, which did not noticeably improve the model fit (P=0.61). The inset shows the same data on an expanded y axis.

Appendix) than those with confirmed myocardial infarction who were enrolled in the trial. Patients with suspected but not confirmed myocardial infarction who were not enrolled in the trial are not recorded in the SWEDEHEART registry, and therefore data for such patients were not available for comparison.

DISCUSSION

This clinical trial involving patients with suspected acute myocardial infarction who did not have hypoxemia at baseline showed no significant effect of supplemental oxygen, as compared with ambient air, on all-cause mortality at 1 year or on the incidence of rehospitalization with myocardial infarction. The absence of an effect of supplemental oxygen on mortality was consistent in all prespecified subgroups, regardless of baseline characteristics or final diagnosis. These findings are consistent with the results of meta-analyses[10,17,18] and are also in accordance with the recently published results of the small (100 patients) Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) trial,[19] in which oxygen was found to have no effect on infarct size.

The AVOID trial of oxygen in acute myocardial infarction enrolled 441 patients with STEMI. The AVOID investigators reported larger myocardial infarcts among the patients who were assigned to receive oxygen than among those who were not assigned to receive oxygen.[9] A larger infarct size due to oxygen could be expected to increase mortality.[20] However, we did not see any effect of oxygen on mortality in the current trial. We also found no difference between the two study groups in the extent of myocardial injury as indicated by cardiac troponin levels, despite a lower incidence of hypoxemia in the oxygen group. The two trials differed in several ways. The DETO2X-AMI trial recruited 15 times as many patients as the AVOID trial. Furthermore, in the DETO2X-AMI trial, we recruited patients with suspected myocardial infarction in the prehospital and hospital

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

Table 3. End Points during and after Hospitalization.

Timing and End Point	Oxygen Group (N=3311)	Ambient-Air Group (N=3318)	Hazard Ratio (95% CI)	P Value
365 Days after randomization				
Death from any cause — no. (%)	166 (5.0)	168 (5.1)	0.97 (0.79–1.21)	0.80
Rehospitalization with myocardial infarction — no. (%)	126 (3.8)	111 (3.3)	1.13 (0.88–1.46)	0.33
Composite of death from any cause or rehospitalization with myocardial infarction — no. (%)	275 (8.3)	264 (8.0)	1.03 (0.87–1.22)	0.70
30 Days after randomization				
Death from any cause — no. (%)	73 (2.2)	67 (2.0)	1.07 (0.77–1.50)	0.67
Rehospitalization with myocardial infarction — no. (%)	45 (1.4)	31 (0.9)	1.46 (0.92–2.31)	0.11
Composite of death from any cause or rehospitalization with myocardial infarction — no. (%)	114 (3.4)	95 (2.9)	1.19 (0.91–1.56)	0.21
During hospital stay				
Median highest measured level of highly sensitive troponin T (IQR) — ng/liter*	946.5 (243.0–2884.0)	983.0 (225.0–2931.0)	—	0.97

* Data were available for 3976 (79.4%) of the 5010 patients with confirmed myocardial infarction: 1998 patients (80.4%) in the oxygen group and 1978 patients (78.3%) in the ambient-air group. The P value for the comparison was calculated with the use of a nonparametric Wilcoxon signed-rank test.

settings, whereas in the AVOID trial only patients with STEMI were enrolled, and all patients were enrolled through the ambulance service. In the DETO2X-AMI trial, we enrolled patients who had an oxygen saturation of 90% or higher, and we administered oxygen at 6 liters per minute through an open face mask, whereas in the AVOID trial a lower limit of 94% oxygen saturation was used, and oxygen was provided at 8 liters per minute through a closed mask.

Several limitations of the present trial warrant consideration. Our trial was an open-label trial; double blinding was not considered to be feasible or ethical, because there is no pressurized air in Swedish ambulances, and the available closed Hudson masks might have put patients at risk for carbon dioxide retention if they had been used as a sham comparator. Clinical and procedural end-point measures were obtained from SWEDEHEART and the Swedish National Population Registry and were not centrally adjudicated. However, the primary end point of death from any cause does not require adjudication. Any degree of uncertainty in other nonadjudicated secondary outcome variables should be equally distributed over the two randomized study groups. Furthermore, the agreement between key variables in the registry and medical records has repeatedly been found to be 95% to 96% when checked by designated registry monitors in the past.[11]

Finally, when the trial was being planned, available sources suggested a 1-year mortality of 14.4% among patients with myocardial infarction, and this value was used in our power calculations.[12] In reality, mortality was substantially lower, for several reasons. The power calculation was based on a cohort of patients from the SWEDEHEART registry, all of whom had a final diagnosis of myocardial infarction that was evaluated independently of levels of oxygen saturation (which are not available in SWEDEHEART), whereas 24.4% of the participants in our trial had other diagnoses, and some of these patients were at lower risk for death than those with myocardial infarction. By design, our trial excluded patients with hypoxemia, but these patients contributed considerably to the total mortality in an unselected population with myocardial infarction. Consequently, the patients with myocardial infarction who did not undergo randomization during the trial period were at higher risk for all the end points we considered and had higher event rates than the patients who were included in our trial. In addition, the informed-consent procedure approved by the ethics committee demanded oral agreement before initiation of the trial. Therefore, patients with altered mental

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.

status were not eligible to participate in the trial. Because power for evaluation of the primary end point was lower than anticipated, we cannot completely rule out a small beneficial or detrimental effect of oxygen on mortality. However, the superimposable time-to-event curves until 12 months, the consistent results in all prespecified subgroups, and the neutral results with regard to the secondary clinical and procedural end points make a clinically relevant difference unlikely.

In conclusion, we conducted a pragmatic, registry-based randomized clinical trial evaluating supplemental oxygen versus ambient air in patients presenting with suspected myocardial infarction who were not hypoxemic at baseline. We did not find a beneficial effect of oxygen treatment with respect to all-cause mortality at 1 year.

Supported by the Swedish Heart–Lung Foundation, the Swedish Research Council, and the Swedish Foundation for Strategic Research.

Dr. Jernberg reports receiving lecture fees and consulting fees from AstraZeneca, consulting fees from Merck Sharp & Dohme, and lecture fees from Aspen; Dr. Lindahl, receiving fees for serving on a steering committee, paid to his university, from Roche, research support and advisory board fees, paid to his university, from BioMerieux, and advisory board fees, paid to his university, from Philips and Thermofisher; and Dr. Erlinge, receiving lecture fees and advisory board fees from AstraZeneca and the Medicines Company. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in the DETO2X-AMI trial; the clinical and research teams of the ambulance service, emergency departments, cardiac intensive care units, catheter laboratories, and cardiology departments for their collaboration and commitment to SWEDEHEART and this trial; and the staff at the Uppsala Clinical Research Center at Uppsala University for administrative and statistical assistance.

APPENDIX

The authors' affiliations are as follows: the Department of Clinical Science and Education, Division of Cardiology (R.H., N.W., M.F.), and Center for Resuscitation Science (L.S.), Karolinska Institutet, Södersjukhuset, and the Department of Clinical Sciences, Cardiology, Danderyd Hospital, Karolinska Institutet (T.J., R.L., M.E.), Stockholm, the Department of Medical Sciences, Cardiology (S.K.J., B.L., G.A.), and Uppsala Clinical Research Center (S.K.J., O.Ö.), Uppsala University, Uppsala, the Department of Clinical Sciences, Cardiology (D.E., D.S.), and Department of Clinical Sciences, Emergency Medicine (U.E.), Lund University, Lund, the Department of Medical and Health Sciences and Department of Cardiology, Linköping University, Linköping (J.A., L.N.), the Department of Cardiology, Sahlgrenska University Hospital, Gothenburg (A.R.-F., E.O., J.H.), the Department of Cardiology, Örebro University Hospital, Örebro (T.K.), the Department of Internal Medicine, Division of Cardiology, Ryhov Hospital, Jönköping (J.L.), the Department of Cardiology, Karlstad Central Hospital, Karlstad (U.H.), the Department of Cardiology, Karolinska University Hospital (J.P.), and the Department of Medicine, Karolinska Institutet (J.P., L.S.), Solna, and the Department of Health Sciences, University of Borås, Borås (J.H.) — all in Sweden.

REFERENCES

1. Steele C. Severe angina pectoris relieved by oxygen inhalations. BMJ 1900;2:1568.
2. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569-619.
3. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.
4. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. Circulation 1975;52:360-8.
5. Madias JE, Madias NE, Hood WB Jr. Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. Circulation 1976;53:411-7.
6. Kelly RF, Hursey TL, Parrillo JE, Schaer GL. Effect of 100% oxygen administration on infarct size and left ventricular function in a canine model of myocardial infarction and reperfusion. Am Heart J 1995;130:957-65.
7. Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol 2010;56:1013-6.
8. Zweier JL, Talukder MAH. The role of oxidants and free radicals in reperfusion injury. Cardiovasc Res 2006;70:181-90.
9. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131:2143-50.
10. Cabello JB, Burls A, Emparanza JI, Bayliss SE, Quinn T. Oxygen therapy for acute myocardial infarction. Cochrane Database Syst Rev 2016;12:CD007160.
11. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Heart 2010;96:1617-21.
12. Hofmann R, James SK, Svensson L, et al. DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial. Am Heart J 2014;167:322-8.
13. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551-67.
14. Thang ND, Karlson BW, Bergman B, et al. Characteristics of and outcome for patients with chest pain in relation to transport by the emergency medical services in a 20-year perspective. Am J Emerg Med 2012;30:1788-95.
15. Thang ND, Karlson BW, Bergman B, et al. Patients admitted to hospital with chest pain — changes in a 20-year perspective. Int J Cardiol 2013;166:141-6.
16. Montori VM, Guyatt GH. Intention-to-treat principle. CMAJ 2001;165:1339-41.
17. Steyerberg EW, Bossuyt PM, Lee KL. Clinical trials in acute myocardial infarction: should we adjust for baseline characteristics? Am Heart J 2000;139:745-51.
18. Sepehrvand N, Ezekowitz JA. Oxygen therapy in patients with acute heart failure: friend or foe? JACC Heart Fail 2016;4:783-90.
19. Khoshnood A, Carlsson M, Akbarzadeh M, et al. Effect of oxygen therapy on myocardial salvage in ST elevation myocardial infarction: the randomized SOCCER trial. Eur J Emerg Med 2016 November 23 (Epub ahead of print).
20. Schömig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. N Engl J Med 2000;343:385-91.

Copyright © 2017 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org on October 30, 2022. For personal use only. No other uses without permission.
Copyright © 2017 Massachusetts Medical Society. All rights reserved.